organic compounds

Oxythiamine hexafluorophosphate monohydrate, a thiamine antagonist with the same conformation as thiamine

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In the title compound, 3-[(3,4-dihydro-2-methyl-4-oxopyrimidin-5-yl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium hexafluorophosphate monohydrate, $C_{12}H_{16}N_3O_2S^+ \cdot PF_6^- \cdot H_2O$, oxythiamine is a monovalent cation with a neutral oxopyrimidine ring. The molecule assumes the F conformation, which is a common form for thiamine but which is substantially different from the unusual V conformation found in the chloride and hydrochloride salts of oxythiamine. The anion-bridging interaction, $C-H \cdots anion \cdots pyrimidine$, is emphasized as being important for stabilization of the F conformation.

Comment

Oxythiamine is a potent antagonist of thiamine (vitamin B$_1$), *i.e.* it competes with thiamine in the catalytic reactions of the metabolic enzymes which require thiamine pyrophosphate as a coenzyme. Oxythiamine pyrophosphate can react with the substrate in place of thiamine pyrophosphate to form a C2-substituted reaction intermediate, but the reaction does not proceed to the release of the final product, thus inhibiting thiamine catalysis (Schellenberger, 1967).

Oxythiamine differs from thiamine only in that an O atom replaces the 4'-amino group. The changes arising from this replacement should be responsible for the inhibitory effects. It has been demonstrated (Shin *et al.*, 1979, 1981) that there are two primary differences between thiamine and oxythiamine structures. Firstly, replacement of the 4'-amino group with an oxo group causes a change in the relative basicity of the ring N atoms; the basicity of N1' is greater than that of N3' in the aminopyrimidine ring, but N3' is more basic than N1' in the oxopyrimidine ring. Secondly, there is a change in the preferred conformation of the pyrimidine and thiazolium rings with respect to the C35' methylene bridge; the F conformation is preferred by C2-free thiamine and the V conformation by

C2-free oxythiamine, where the conformations are defined in terms of the torsion angles φ_T (C5'—C35'—N3—C2) of $0°$ and φ_P (N3—C35'—C5'—C4') of $\pm 90°$ for the F form, and φ_T of $\pm 90°$ and φ_P of $\pm 90°$ for the V form (Pletcher *et al.*, 1977). However, we recently reported the first X-ray evidence that C2-free oxythiamine in the structures of its hexachloroplatinate and decavanadate salts adopts the F form rather than the V form and suggested that anions play an important role in stabilizing the molecular conformation (Hu *et al.*, 1999). The purpose of the present study of oxythiamine hexafluorophosphate monohydrate, (I), is to examine further the conformational properties of oxythiamine and the interactions of oxythiamine with anions, and to compare them with those of thiamine.

(I)
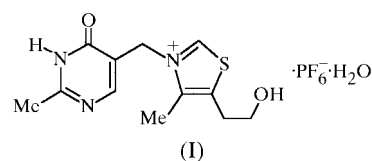
The molecular dimensions of oxythiamine in (I) (Table 1) agree well with those in oxythiamine chloride dihydrate (Shin *et al.*, 1981). The structure analysis shows that oxythiamine exists as a monovalent cation with a neutral pyrimidine ring. The H atom is bonded to N3' instead of N1'. The differences between the neutral oxopyrimidine ring and the protonated form are mainly manifested by the N1'—C2' and C2'—N3' bonds, and the C2'—N1'—C6' angle. The N1'—C2' bond [1.310 (3) Å] is shorter than the C2'—N3' bond [1.347 (3) Å] in the neutral ring, whereas they are approximately equal in the protonated ring (Shin *et al.*, 1979). The C2'—N1'—C6' angle becomes larger when the ring is protonated at N1'. The C5 hydroxyethyl side chain is folded back towards the thiazolium ring to make a close contact between O53 and electropositive S1 atom (Jordan, 1974), with O53$\cdots$S1 = 3.034 (2) Å and the torsion angles $\varphi_{5\alpha}$ (S1—C5—C51—C52) = 63.4 (3)$°$ and $\varphi_{5\beta}$ (C5—C51—C52—O53) = −71.4 (3)$°$.

The interesting result of this work is that the oxythiamine molecule adopts the F conformation with φ_T = 9.7 (3)$°$ and φ_P = 80.5 (3)$°$, the same as that reported for most of the thiamine structures (Louloudi & Hadjiliadis, 1994). This conformation is characterized by the C2—H2 bond pointing over the pyrimidine, with a distance of 2.49 (3) Å between H2 and the pyrimidine ring plane. This is an additional example of the conformational variability of oxythiamine. In addition to the V form, oxythiamine also assumes other conformations; the F form in (I) and in the hexachloroplatinate and decavanadate salts, and a novel V' form in the picrolonate salt (Hu *et al.*, 1999).

What are the main factors influencing these conformations? In the crystal structure of the thiamine-dependent enzyme pyruvate decarboxylase (Dyda *et al.*, 1993), the V conformation of thiamine pyrophosphate is stabilized by strong van der Waals interactions with the side chain of an isoleucine residue which is wedged between the thiazolium and pyrimidine rings. Aoki *et al.* (1991, 1993) have observed that two types of anion bridges between the thiazolium and pyrimidine rings of a

thiamine molecule occur frequently in thiamine compounds with the F form. We define a type I anion bridge to be of the form C2—H···anion···pyrimidine and a type II anion bridge to be of the form N4′1—H···anion···thiazolium. Both type I and type II anion bridges exist in thiamine·PF$_6$·H$_2$O, which adopts the F conformation (Aoki *et al.*, 1988). In the structure of (I), although the type II anion bridge is absent because of the change in the hydrogen-bonding scheme caused by substitution of 4′-amino by an oxo group, the type I anion bridge is again found (Fig. 1); the C2 atom forms a bifurcated hydrogen bond with F3 and F4 of the anion (Table 3), which makes close contacts with the pyrimidine ring, the closest distance being F4···N3′ of 3.183 (3) Å (Table 2). Type I anion bridges have also been observed in the hexachloroplatinate and decavanadate salts of oxythiamine. These results further support the conclusion from the study of thiamine structures (Aoki *et al.*, 1991) that the type I anion bridge is an important determinant of the F conformation. Widespread occurrence of the type I anion bridge in either thiamine or oxythiamine compounds suggests it is likely that an anionic or electronegative group from an amino acid residue in thiamine-binding proteins (Iwashima & Nishimura, 1979) is located in the vicinity of the C2 site and is stabilized by this type of interaction when thiamine is in the F form.

It is of interest to note that, to a certain extent, the molecular conformation is correlated with packing modes. For example, the molecular association in a hydrogen-bonded cyclic dimer is one of the structural features of thiamine compounds with the F form, sometimes resulting in supramolecular structures (Aoki *et al.*, 1993). The hexachloroplatinate salt of oxythiamine in the F form also shows such a cyclic dimeric structure. In the structure of (I), as shown in Fig. 2, a 'head-to-tail' ('head' is the pyrimidine ring and 'tail' is the hydroxyethyl side chain) cyclic dimer that involves two PF$_6^-$ ions at the positions of the type I anion bridge is formed
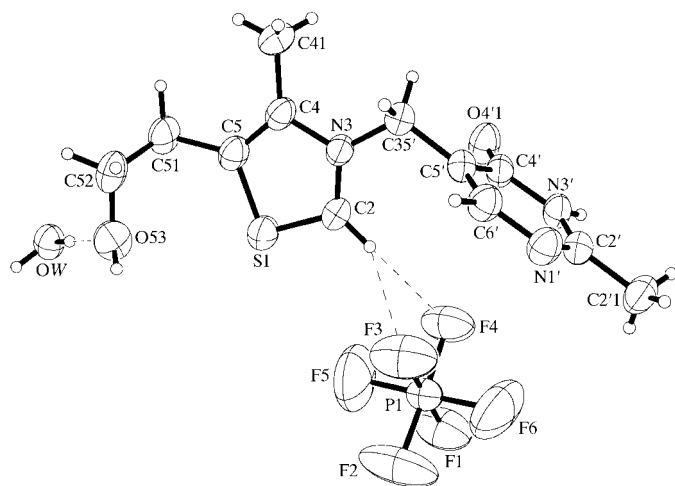
through a pair of O53—H···N1′ hydrogen bonds. The dimers are linked in the b direction by hydrogen bonds involving the water molecules and are arranged in the c direction to form a molecular column, with the PF$_6^-$ ions sandwiched between the thiazolium rings. Table 2 lists the close contacts of a PF$_6^-$ anion with these two thiazolium rings.
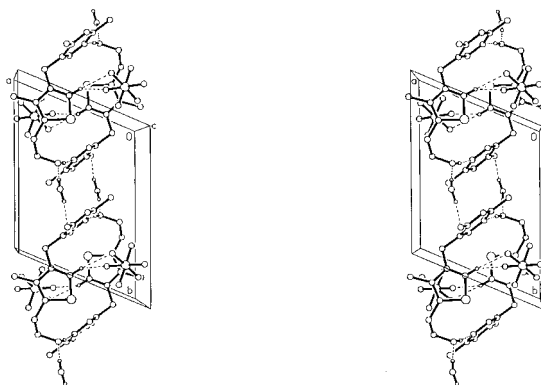

Figure 2
A stereoview of the crystal packing in (I), showing the formation of the hydrogen-bonded cyclic dimer and the interactions between the anions and the dimers. Only those H atoms involved in hydrogen bonds are shown. Broken lines denote hydrogen bonds.

Experimental

Aqueous solutions of oxythiamine chloride hydrochloride (Sigma Chemical Co.; 169.2 mg, 0.5 mmol) and NH$_4$PF$_6$ (Kanto Chemical Co.; 407.5 mg, 2.5 mmol) were mixed (pH 2). The pH value was adjusted to 7 using a 1N NaOH solution. Crystals of (I) were obtained from the resulting solution after several days.

Crystal data

C$_{12}$H$_{16}$N$_3$O$_2$S$^+$·PF$_6^-$·H$_2$O	$Z = 2$
$M_r = 429.32$	$D_x = 1.586$ Mg m^{-3}
Triclinic, $P\bar{1}$	Mo $K\alpha$ radiation
$a = 9.2881$ (12) Å	Cell parameters from 24
$b = 11.9318$ (13) Å	reflections
$c = 8.8201$ (7) Å	$\theta = 14.87–14.99°$
$\alpha = 91.607$ (8)°	$\mu = 0.346$ mm^{-1}
$\beta = 92.081$ (9)°	$T = 293$ (2) K
$\gamma = 112.925$ (9)°	Tabular, colourless
$V = 898.73$ (17) Å^3	$0.40 \times 0.35 \times 0.15$ mm

Data collection

Rigaku AFC-7R diffractometer	$h = -2 \rightarrow 12$
$\omega/2\theta$ scans	$k = -15 \rightarrow 14$
4485 measured reflections	$l = -11 \rightarrow 11$
4133 independent reflections	3 standard reflections
3430 reflections with $I > 2\sigma(I)$	every 150 reflections
$R_{int} = 0.005$	intensity decay: none
$\theta_{max} = 27.5°$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0794P)^2$
$R[F^2 > 2\sigma(F^2)] = 0.051$	$+ 0.5230P]$
$wR(F^2) = 0.154$	where $P(F_o^2 + 2F_c^2)/3$
$S = 1.069$	$(\Delta/\sigma)_{max} = 0.004$
4133 reflections	$\Delta\rho_{max} = 0.59$ e Å^{-3}
299 parameters	$\Delta\rho_{min} = -0.37$ e Å^{-3}
H atoms treated by a mixture of independent and constrained refinement	

Figure 1
The structure of (I) showing 50% probability displacement ellipsoids. Note that the PF$_6^-$ anion interacts with oxythiamine through a bifurcated hydrogen bond, C2—H···F3 and C2—H···F4, and close contacts, F3···pyrimidine and F4···pyrimidine. Broken lines denote hydrogen bonds. H atoms are drawn as small spheres of arbitrary radii.

Table 1
Selected geometric parameters (Å, °).

S1—C2	1.670 (2)	C35′—C5′	1.497 (3)
S1—C5	1.725 (2)	N1′—C2′	1.310 (3)
C2—N3	1.316 (3)	N1′—C6′	1.366 (3)
N3—C4	1.397 (3)	C2′—N3′	1.347 (3)
N3—C35′	1.482 (3)	C2′—C2′1	1.490 (3)
C4—C5	1.345 (4)	N3′—C4′	1.384 (3)
C4—C41	1.493 (4)	C4′—O4′1	1.228 (3)
C5—C51	1.500 (3)	C4′—C5′	1.439 (3)
C51—C52	1.520 (4)	C5′—C6′	1.352 (3)
C52—O53	1.423 (4)		
C2—S1—C5	91.04 (12)	N3—C35′—C5′	113.17 (19)
N3—C2—S1	112.72 (17)	C2′—N1′—C6′	116.3 (2)
C2—N3—C4	113.7 (2)	N1′—C2′—N3′	122.6 (2)
C2—N3—C35′	124.18 (19)	N1′—C2′—C2′1	120.3 (2)
C4—N3—C35′	121.89 (19)	N3′—C2′—C2′1	117.1 (2)
C5—C4—N3	111.6 (2)	C2′—N3′—C4′	123.9 (2)
C5—C4—C41	128.2 (2)	O4′1—C4′—N3′	121.4 (2)
N3—C4—C41	120.2 (2)	O4′1—C4′—C5′	125.1 (2)
C4—C5—C51	127.9 (2)	N3′—C4′—C5′	113.51 (19)
C4—C5—S1	110.86 (16)	C6′—C5′—C4′	118.7 (2)
C51—C5—S1	121.1 (2)	C6′—C5′—C35′	123.1 (2)
C5—C51—C52	111.3 (2)	C4′—C5′—C35′	118.1 (2)
O53—C52—C51	109.4 (2)	C5′—C6′—N1′	124.9 (2)

Table 2
Contact distances (Å).

S1···O53	3.034 (2)	C2···F3^i	3.202 (3)
N1′···F3	3.481 (3)	N3···F3^i	3.140 (3)
C6′···F3	3.396 (4)	C4···F3^i	3.417 (3)
C2′···F4	3.360 (3)	C4···F2^i	3.388 (3)
N3′···F4	3.183 (3)	S1···F4^{ii}	3.664 (2)
C4′···F4	3.272 (3)	C5···F4^{ii}	3.431 (3)

Symmetry codes: (i) $1 - x, 2 - y, 1 - z$; (ii) $1 - x, 2 - y, -z$.

All H atoms were located from difference Fourier maps and were refined isotropically, except for the H atoms of water (HW1 and HW2) which were fixed in the refinements with an isotropic displacement parameter of 0.06 Å^2.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1985); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *MSC/AFC Diffractometer Control Software*; program(s) used to solve structure:

Table 3
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C2—H2···F3	0.94 (3)	2.51 (3)	3.321 (4)	145 (2)
C2—H2···F4	0.94 (3)	2.33 (3)	3.204 (3)	156 (2)
O53—H53···N1′^{i}	0.840 (19)	1.94 (2)	2.779 (3)	172 (5)
N3′—H3′···OW^{ii}	0.88 (3)	1.88 (3)	2.752 (3)	176 (3)
OW—HW1···O53	1.04	1.69	2.726 (3)	174
OW—HW2···O4′1^{iii}	0.87	1.97	2.808 (3)	163

Symmetry codes: (i) $1 - x, 2 - y, 1 - z$; (ii) $1 - x, 2 - y, -z$; (iii) $x, y - 1, z$.

*SHELXS*86 (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1104). Services for accessing these data are described at the back of the journal.

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